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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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SUEDE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
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Use of ghrelin for treating low body weight and body fat in gastrectomized individuals

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Applicant: John-Olov Jansson
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Use of ghrelin for treating low body weight and body fat in gastrectomized individuals

The present invention relates to the use of ghrelin or analogues thereof for treating malnutrition in an individual having been subjected to gastrectomy. Specifically, the instant invention pertains to the use of ghrelin or analogues thereof for increasing body weight, body fat mass, appetite and well being in a gastrectomized individual.

The stomach is supposed to have several important functions such initial storage of food digestion of food by mixing it with acid and pepsin. Thereafter the food gradually is released at a steady rate into the small intestine. A number of patients around the world have been subjected to gastrectomy for different indications. Most of them have undergone surgery because of ventricle cancer, and a few patients because of gastric ulcer, especially after severe bleeding or rupture. A variety of different types of gastrectomy surgery have been performed throughout the years. One type used for the treatment of gastric ulcer was antrum resection in combination with selective vagotomy. In addition, surgery according to Billroth I and II, which includes resection of the antrum, was used for the treatment of gastric ulcers. Another type of surgery used to treat ventricle cancer was complete ventricle resection with a so-called Roux-en-Y, oesophago-jejunostomi. Gastrectomy, especially complete ventricle resection with Roux-en-Y, results in section of extragastric vagal nerves. At present, more than three quarters of all patients who have undergone surgery for gastric cancer, have been subjected to total gastrectomy.

Even though gastrectomy may provide a remedy for cancer or complications of gastric ulcer, it is accompanied by a variety of subsequent disorders. In these patients it has been observed that both, subtotal and total gastrectomy result in a loss of body weight of about 10% within the first six months after surgery, which loss was shown to be mainly due to a loss of body fat, with body cell mass and muscle mass essentially remaining unchanged (Liedman et al.,

World J Surg 21, (1997), 416-20. Also loss of appetite and malabsorption has been noted which is assumed to contribute to the weight loss.

In addition, gastrectomized patients suffer from fatigue, osteoporosis and also diarrhea, which is presumed to originate from a diminished capability to absorb fat. Moreover, anemia is observed which is caused by a decreased absorption of iron and lack of vitamin B_{12}, the latter being due to lack of an intrinsic factor, which is normally produced in the stomach.

Even though gastrectomized patients are routinely given replacement therapy with vitamin B_{12}, iron, and calcium, they continue to suffer from fatigue, loss of fat mass and osteoporosis (Fischer et al, Complications of Surgery, In: Schwartz (Ed), Principles of surgery, (1999), Seventh ed, McGraw-Hill, New York, pp 470-472). A possible remaining problem would be the loss of the place for initial storage and digestion of the ingested food.

Therefore, a problem of the present invention resides in alleviating the symptoms gastrectomized patients encounter after surgery, in particular to provide means to obviate the patient's deficiency to keep body weight and body fat.

This problem has been solved by providing the use of ghrelin or an analogue thereof for the preparation of a medicament for the treatment of loss of body weight and body fat in a gastrectomized individual.

In the figures,

Fig. 1 graphically shows that treatment of gastrectomised rats with the GH secretagogue MK677 increased body weight;

Fig. 2 graphically shows that the treated animals show a higher fat pad weight;

Fig. 3 shows that treatment of gastrectomised rats with the GH secretagogue MK677 increased NPY mRNA levels in the hypothalamus.

Ghrelin is a peptide of 28 amino acids in length, which has been isolated in the stomach in humans in a specific cell type, namely in the so-called A-cells, which are mainly located in the oxyntic glands in the corpus and fundus. They contain an octanoyl ester attached to a serine residue (Kojima et al, Nature, **402,** (1999), 656-660). Ghrelin and its analogues are known to be releasers of growth hormone in animals and man. These peptides act via a 7-transmembrane G-protein coupled receptor which is present both in the hypothalamus and in the pituitary (Smith et al Endocr Rev **18,** (1997), 621-45).

It is known that total gastrectomy of humans reduces circulating ghrelin levels to about 30% of those in normal individuals (Ariyasu et al., J. Clin Endocrinol Metab **86** (2001), 4753-4817). In rats, the ghrelin levels in circulation were lowered to about 20% of normal after surgical removal of the acid producing rumen and fundus parts of the stomach (Dornonville de la Cour et al., Regul. Pept. **99** (2001), 141-150).

Ghrelin is reported to locally act in the gastrointestinal tract, in particular the stomach, since it has been found to stimulate gastric acid production and gastrointestinal motility (Asakawa et al., Gastroenterology **120** (2001), 337-345; Masuda et al., Biochem Biophys Res. Commun. **276** (2000), 905-908). Even though ghrelin has been found to be an appetite stimulatory signal, it has been noted that this stimulatory effect is lost after vagotomy (Asakawa , supra), giving rise to the notion that for a proper action of ghrelin the presence of the stomach is required.

In contrast to the general belief, the present inventors have now found that ghrelin and its analogues are still effective in gastrectomized individuals, where potential local effects in the stomach do not operate. These findings are surprising as it has been reported that the stimulation of feeding and hypothalamic NPY expression by ghrelin analogues is dependent on intact vagal innervation (Asakawa, supra).

The present invention also embraces the use of ghrelin analogues. In the context of the present application, analogues to ghrelin are to be understood as any peptide or non-peptide

compound that essentially exerts the same biological effect as ghrelin in vivo. Exemplary non-peptide ghrelin analogues are described in EP 0 869 974 and EP 1 060 190, which illustrate a number of ghrelin analogues and which documents are incorporated herein by way of reference.

According to the present invention ghrelin may be utilized as the well-known 27 or 28 amino acid peptide and may be produced by chemical synthesis or recombinant techniques. Techniques for producing peptides and linking an octanoyl ester to the serine no. 3 are well within the technical person's skill. Alternatively any of the analogues mentioned in the documents referred to above may be utilized. Preferred compounds are the compounds designated as NN 703 [5-Amino-5-methylex-2-enoic acid N-methyl-N-((1R)-1-(methyl-((1R)-1-(methylcarbamoyl-2-phenylethylcarbomoyl)-2-(naphtalen-2-yl)ethyl)amide] and MK677 [sometimes also designated MKO677, cf. Drug Discovery Today, vol. 4, No.11, November 1999, 497-506] or NNC 26-1291, or NNC 26-1187 are growth hormone secretagogues of a non-peptidyl described in WO 99/58501 and WO 00/26252, respectively, all of which documents are incorporated herein by way of reference.

In summary, the present invention provides a method for chronic treatment of body weight loss, fat mass loss etc., occurring after gastrectomy, wherein a pharmaceutically effective amount of a substance, that upon administration to a gastrectomized patient leads to an increased level of a ghrelin receptor agonist, is administered to a patient.

Preferably, the treatment comprises increasing the appetite in the individual and increasing the body fat mass of the individual, which will eventually improve the sense of well being and the quality of life in the individual.

In addition, ghrelin and/or its analogues may also be utilized in combination with another stomach derived factor, so as to improve the results observed. Exemplarily mentioned factors are gastrin and pancreastatin.

Furthermore, the invention relates to a composition comprising ghrelin or an analogue

thereof for treating malnutrition in an gastrectomized individual, in particular for increasing his appetite, body weight, specifically his body fat mass, and eventually his well being.

The composition will contain the active ingredient together with a pharmaceutically acceptable carrier or diluent, which will be selected by the skilled artisan according to the route of administration. The pharmaceutical carrier or diluent employed may be a conventional solid or liquid carrier, e.g. lactose, cyclodextrin, talc, gelatin, agar, pectin, magnesium stearate, cellulose-derivatives, or syrup, olive oil, phospholipids, polyoxyethylene or simply water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or admixed with one or more waxes. The compositions may appear in conventional forms, such as capsules, tablets, aerosols, solutions, suspensions or topical applications.

For the present indication the dosage will vary depending on the compound employed and the mode of administration. Dosage levels will vary between about 0.1 to 10 mg/kg body weight daily, preferably between about 0.3 to 7 mg/kg body weight, more preferably between 0.5 to 5 mg/kg body weight. The route of administration may be any route which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral, the oral or pulmonar route being preferred.

The objective compounds may be administered as a pharmaceutically acceptable acid addition salt or, where appropriate, as a alkali metal or alkaline earth metal or lower alkylammonium salt. Such salt forms are believed to exhibit approximately the same order of activity as the free base forms. Suitable dosages may range from about 50 mg to about 200 mg, preferably from about 20 mg to about 100 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

The following example illustrates the invention without limiting it thereto.

Example

Total gastrectomy was performed and followed by end-to-end anastomosis between the esophagus and the duodenum as described in Lehto-Axtelius D., et al. Osteopenia after gastrectomy, fundectomy or antrectomy: an experimental study in the rat., Regul. Pept. **78** (1998), 41-50. The gastrectomy was accompanied by total vagotomy at the level of cardia. Sham operation was performed by opening the abdomen and moving the stomach.

In sham gastrectomised rats the ghrelin levels were 2.06± 0.22 ng/ml, while they were less than the least detectable level of the assay, i e, 0.25 ng/ml after gastrectomy. From four weeks after gastrectomy the animals were administered either water or the ghrelin analogue MK-0677 by gavage once daily (4 mg/kg/day).

Food intake and body weight was measured daily and throughout the experiment. Animals treated with ghrelin showed an increased desire for food. After two weeks of treatment, the animals were decapitated and blood and tissues collected and rapidly frozen. Gonadal, mesenteric and retroperitoneal far pads were dissected and weighed, and the sum of the weight was then calculated. Ghrelin was measured in serum using a kit purchased from Phoenix Pharmaceuticals as described (Dornonville de la Cour, supra).

Treatment of gastrectomised rats with the GH secretagogue MK677, surprisingly, increased body weight. Moreover, this treatment resulted in enhanced weight of the sum of dissected fat pad weights, and increased hypothalamic levels of NPY mRNA.

Claims

1. Use of ghrelin or an analogue thereof for the preparation of a medicament for the treatment of loss of body weight and body fat of a gastrectomized individual.

2. The use according to claim 1, wherein the treatment stimulates appetite and prevents malnutrition of the individual.

3. The use according to claim 1, wherein the treatment comprises improving the sense of well being and the quality of life in the individual.

4. The use according to any of the preceding claims in combination with another stomach derived factor.

5. The use according to any of the preceding claims, wherein the active compound is administered in a dose of from about 0.1 mg/kg bodyweight/day to about 10 mg/kg/day, preferably from about 0.5 to 5 mg/kg/day.

6. A composition comprising ghrelin or an analogue thereof for the treatment of loss of body weight and body fat in a gastrectomized individual.

7. The composition according to claim 6 for increasing the appetite, the sense of well being, and the quality of life, and decreasing malnutrition in a gastrectomized individual.

8. The composition according to any of the claims 6 or 7, which comprises a pharmaceutically acceptable carrier or a diluent.

9. The composition according to any of the claims 6 to 8 in unit dosage form, comprising from about 5 to about 250 mg of the ghrelin or an analogue thereof or a pharmaceutically acceptable salt thereof.

10. The composition according to any of the claims 6 to 9 for oral, nasal, transdermal, pulmonal, or parenteral administration.

Summary

The present invention relates to the use of ghrelin or analogues thereof for treating the symptoms of malnutrition in an individual having been subjected to gastrectomy. Specifically, the instant invention pertains to the use of ghrelin or analogues or secretagogues thereof for increasing body weight, body fat mass, appetite and the well being in an gastrectomized individual.

Fig 1

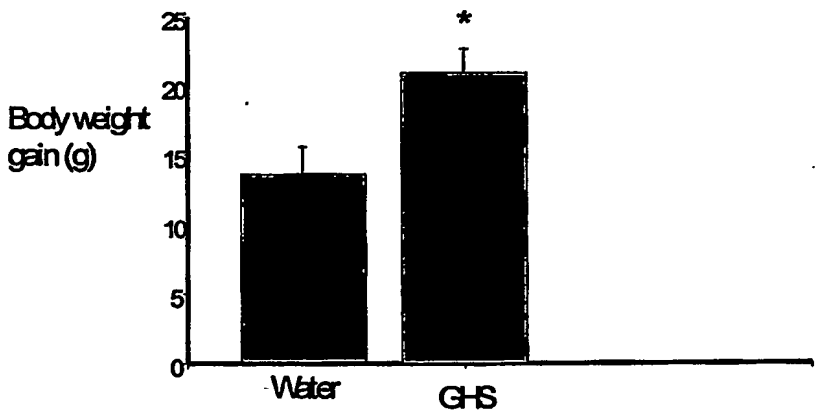


Fig 2

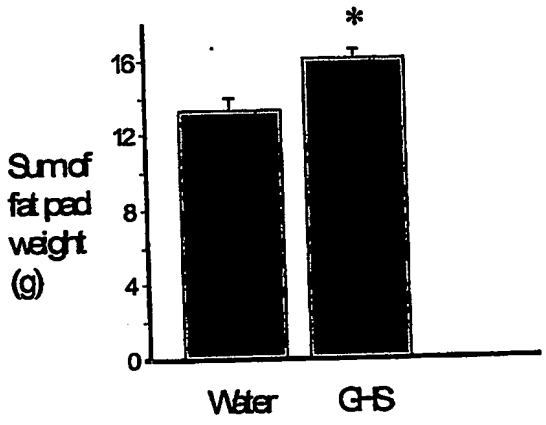
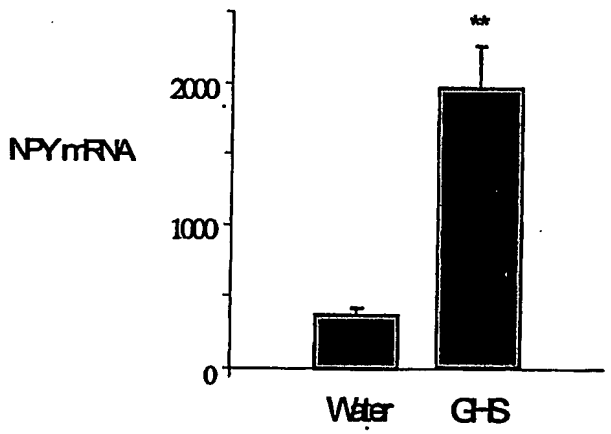


Fig3



5